PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing *(day/month/year)* see form PCT/ISA/210 (second sheet)	
Applicant's or agent's file reference see form PCT/ISA/220	**FOR FURTHER ACTION** See paragraph 2 below
International application No. PCT/EP2004/006265	International filing date *(day/month/year)* 09.06.2004
Priority date *(day/month/year)* 10.06.2003	
International Patent Classification (IPC) or both national classification and IPC C07K14/47, A61K38/17	
Applicant XANTOS BIOMEDICINE AG	

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☒ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☒ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

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WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2004/006265

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was field, unless otherwise indicated under this item.

   ☐ This opinion has been established on the basis of a translation from the original language into the following language .

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☒ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☒ in written format

      ☒ in computer readable form

   c. time of filing/furnishing:

      ☒ contained in the international application as filed.

      ☐ filed together with the international application in computer readable form.

      ☒ furnished subsequently to this Authority for the purposes of search.

3. ☒ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☐ The following document has not been furnished:

   ☐ copy of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(a)).

   ☐ translation of the earlier application whose priority has been claimed (Rule 43*bis*.1 and 66.7(b)).

   Consequently it has not been possible to consider the validity of the priority claim. This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. ☒ The International Searching Authority has not been able to consider the validity of the priority claim because a copy of the earlier application whose priority has been claimed was not available to the International Searching Authority at the time that the search was conducted (Rule 17.1). This opinion has nevertheless been established on the assumption that the relevant date is the claimed priority date.

4. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 12-18 (IA)

because:

☒ the said international application, or the said claims Nos. 12-18 (IA) relate to the following subject matter which does not require an international preliminary examination *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the whole application or for said claims Nos.

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form ☐ has not been furnished

☐ does not comply with the standard

the computer readable form ☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	10,16
	No:	Claims	1-9,11-15,17-19
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-19
Industrial applicability (IA)	Yes:	Claims	1-11,19
	No:	Claims	

2. Citations and explanations

see separate sheet

Box No. VI Certain documents cited

1. Certain published documents (Rules 43*bis*.1 and 70.10)

and / or

2. Non-written disclosures (Rules 43*bis*.1 and 70.9)

see form 210

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (SEPARATE SHEET)

International application No. PCT/EP2004/006265

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 12-18 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

Reasoned statement with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 02/053737 A (NAGANO YUKIKO ; HONDA GOICHI (JP); MATSUDA AKIO (JP); MURAMATSU SHUJI) 11 July 2002 (2002-07-11)

D2: WO 99/06552 A (GENSET SA ; LACROIX BRUNO (FR); DUCLERT AYMERIC (FR); DUMAS MILNE EDWA) 11 February 1999 (1999-02-11)

D3: DATABASE EMBL EBI; 4 January 2002 (2002-01-04), STRAUSBERG RL ET AL.: "Mus musculus RIKEN cDNA D430028G21 gene, mRNA (cDNA clone MGC:25836 IMAGE:4190175), complete CDs." XP002297872 Database accession no. BC020006

D4: DATABASE EMBL EBI; 30 January 2003 (2003-01-30), STRAUSBERG RL ET AL.: "Homo sapiens KIAA1271 protein, mRNA (cDNA clone MGC:50830 IMAGE:5751684), complete CDs." XP002297873 Database accession no. BC0044952

D5: MATSUDA AKIO ET AL: "Large-scale identification and characterization of human genes that activate NF-kappaB and MAPK signaling pathways." ONCOGENE. 22 MAY 2003, vol. 22, no. 21, 22 May 2003 (2003-05-22), pages 3307-3318, XP002297871 ISSN: 0950-9232

D6: THOMPSON J D: "Applications of antisense and siRNAs during preclinical drug development" DRUG DISCOVERY TODAY, ELSEVIER SCIENCE LTD, GB, vol. 7, no. 17, 1 September 2002 (2002-09-01), pages 912-917, XP002236964 ISSN: 1359-6446

D7: WO 03/048202 A (MATSUDA AKIO ; MURAMATSU SHUJI (JP); ASAHI CHEMICAL IND (JP)) 12 June 2003 (2003-06-12)

The present application relates to a human gene and protein, as well as a human isoform and a mouse orthologue, that promotes angiogenic (growth of new capillaries from existing ones) activity in certain cell types. Induces the production of VEGF and expression of other pro-angiogenic factors in HEK293 cells such as IL-8 and RANTES. Several inhibitors of the proteins are shown A.O. inhibitory antibodies (polyclonal and monoclonal, as well as fragments) and a short peptide derived from the extracellular domain. The claims relate to inhibitors to the above genes and proteins.

D1 discloses the cloning of human genes and the encoded proteins that activate NFkB function. SEQ ID NO: 170 has 51% identity with SEQ ID 2, 99.4% identity with SEQ ID 4 and 100% identity with SEQ ID 6 e.g. of a protein falling under the scope of claims 1-5. Use in cancer and ischemic disorders therapy is disclosed. Also disclosed are diagnostic materials (antibodies) for detecting A.O. cancers. Moreover are disclosed peptide and antibody inhibitors, as well as small molecule inhibitors, inhibitory antisense nucleotides, ribozymes and triplex forming nucleotides and antagonists of the genes and proteins in question. D2 discloses the cloning and sequencing of 5' EST's of secreted proteins. SEQ ID NO: 153 has 100% identity in 61 amino acids with sequences SEQ ID 4 and 6 and shows clearly the secretion signal as well as 25 amino acids of the secreted form. This demonstrates that the proteins of SEQ ID 4 and 6 were known to be secreted proteins and that a gene and protein of D2 is falling under the scope of claims 1-5. Also disclosed are antibody inhibitors, as well as inhibitory antisense nucleotides and triplex forming nucleotides. Hence D1 and D2 anticipate novelty of claims 1-7 and also 9, 11-15, 17-19.

Claim 8, with respect to SEQ ID NO's 26 and 27 can be considered novel. However this is only an optional feature and the claim relates to a fragment of "SEP" (whatever this means, see also below) inhibiting "sSEP". There is no structural limitation with respect to length and sequence of the peptides disclosed and so this information is considered in nothing more relevant than say a generic peptide or protein of D1 inhibiting function of SEQ ID 170 of D1. For the moment therefore claim 8 is not considered novel over D1.

In conclusion, D1 and D2 anticipate novelty of claims 1-9, 11-15, 17-19 which are thus not in accordance with Article 33(2) PCT and also not based on inventive step contrary to the requirements of Article 33(3) PCT.

At present is also not apparent in how far claims 10 and 16 e.g use of an inhibitor of "SEP"

in conjunction with an inhibitor of VEGF, which is to be considered novel under Article 33(2) PCT in view of the prior art documents on file, would be based on inventive step as no such inhibitor mix is shown to be of any use or to have any effect. Hence, claims 10 and 16 are not considered to be based in inventive step contrary to Article 33(3) PCT.

Also the inhibitor in connection with full-length SEQ ID 4 and SEQ ID 6 is not considered inventive since D3-D5 disclose to 100% these sequences and a simple combination with e.g. D1 and D2 would have shown the relatedness of theses sequences and the possibility to apply the inhibitors of D1 and D2 to these sequences. Furthermore the siRNA embodiment in claim 6 not considered build on inventive step since D6 shows the usefulness to the skilled person for using antisense oligonucleotides and siRNA in knocking-out gene function. So even if this is not specifically mentioned in D1 and D2 it something obvious to propose for an alternative inhibitor for a skilled person wishing to knock out gene function of a gene, of the sequences indicated above, of D1 and D2.

Re Item VI

Certain documents cited

D7 cited P,X in the search report discloses the cloning of human and mouse genes and the encoded proteins that activate NFkB function. SEQ ID NO: 44 (mouse) has 100% identity with SEQ ID 2, 51% identity with SEQ ID 4 and 51% identity with SEQ ID 6. SEQ ID NO: 46 (human) has 51% identity with SEQ ID 2, 99.4% identity with SEQ ID 4 and 100% identity with SEQ ID 6. Use in cancer and ischemic disorders therapy is disclosed. Also disclosed are diagnostic materials (antibodies, DNA's and others) for detecting A.O. cancers. Moreover are disclosed peptide and antibody inhibitors, as well as small molecule inhibitors, inhibitory antisense nucleotides, ribozymes and triplex forming nucleotides and antagonists. D7 is relevant for novelty of claims 1-9, 11-15, 17-19.

Re Item VIII

Certain observations on the international application

Article 6 PCT (clarity issues).

Throughout the claims the term "inhibitor of sSEP" is used without giving any structural

indication to what such an inhibitor would be. This clearly describes a desideratum but not a solution to a technical problem.

The terms SEP and sSEP used in the claims are private protein designations that have no recognised meaning in the art. Hence they are prone to subjective interpretation and utmost unclear.

The terms "functional active soluble derivative" or "functional active variant" used throughout the claims is totally unclear since it is not apparent for the claims what structure and or function is to be imposed on such a derivative in order for it to be encompassed or not within the claim.

Claims 6 and 8 relate to "fragments of SEP" that neither defined by sequence nor by a minimal length of one of the proteins of the application. It cannot be appreciated what falls under the scope of such a claim.

The term "homology of at least 25%" in claim 2 is unclear. There are dozens of different models for appreciating protein homology, nonetheless it is not specified in the claims which method is used for appreciating the homology.

Claims 17 and 19 relate to "SEP" not defined by any sequence. This is unclear as set out above and moreover prone to subjective interpretation (what is SEP and what not?).